Synthetic Approach to Coumarin Derivatives Through C-H Activation

A Dissertation

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FOR THE DEGREE OF

MASTER OF SCIENCE IN CHEMISTRY

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NATIONAL INSTITUTE OF TECHNOLOGY, ROURKELA

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ROURKELA

CERTIFICATE

This is to certify that the dissertation entitled "**Synthetic Approach To Coumarin Derivatives Through C-H Activation"** being submitted by **Ms**. **Bipasa Halder** for the award of Master of Science in Chemistry. This report includes the work done during the period of August 2014- April 2015 in the Department of Chemistry, National Institute of Technology, Rourkela under my supervision. This work has not been previously submitted for any degree in this/ any other institute.

Place:
Date:

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Associate Professor
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Bipasa Halder

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INTRODUCTION AND LITERATURE SURVEY

Coumarins are a family of naturally occurring compounds. Coumarin motifs are present in numerous natural products such as dicoumaral, querecetin, geiparvain etc. (Figure 1). This class of compounds also exhibit promising biological properties such as anti-inflammatory and antipyretic,[1] antioxidant,[2,3] bronchodilator,[4] vasodilator,[5] antiameoebic,[6] antibacterial[7] and antifungal[8] activities. Coumarins and their derivatives are also used in cosmetics, perfumery and polymer industries. These features have elicited increasing interest in exploring more and efficient methods for their synthesis. Several classical methods involving Perkin reaction, Wittig reaction, Pechmann, Reformatsky etc. have been developed for the successful synthesis of coumarin derivatives. These are methods are summarized in Scheme 1.

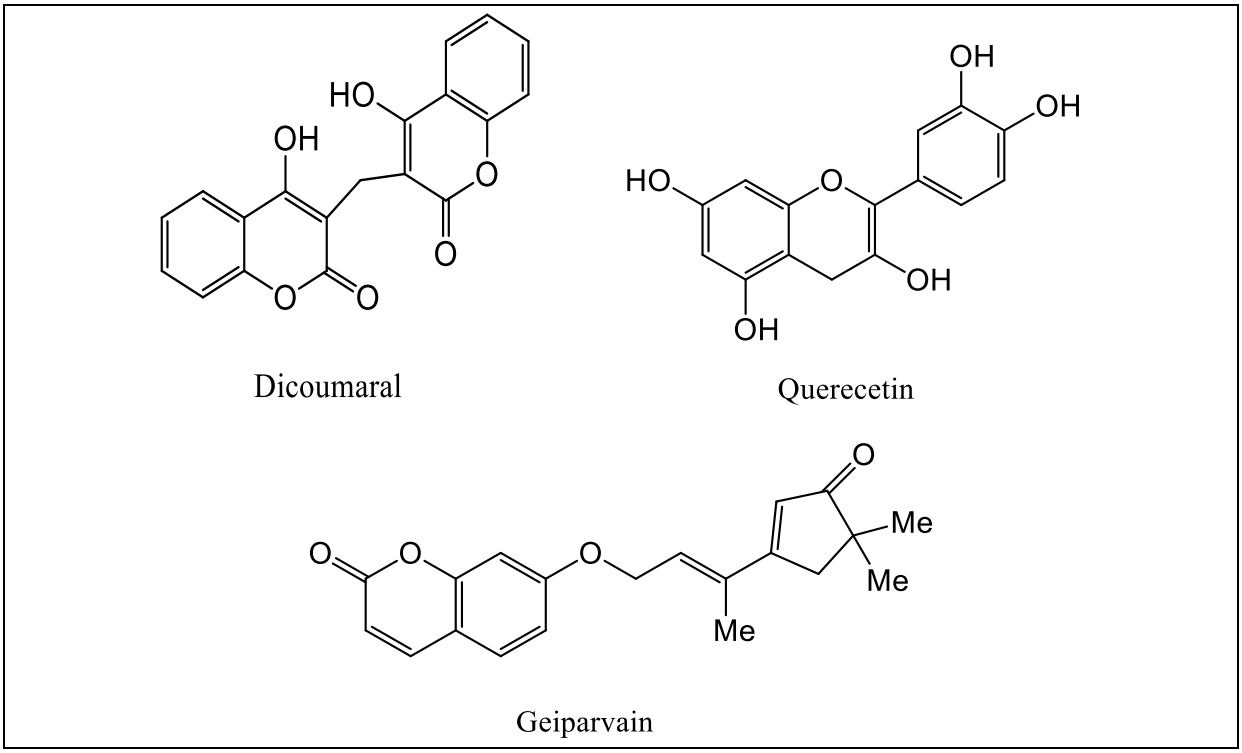
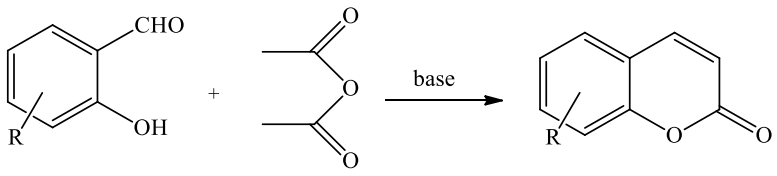


Figure 1: Examples of natural product coumarin derivatives.

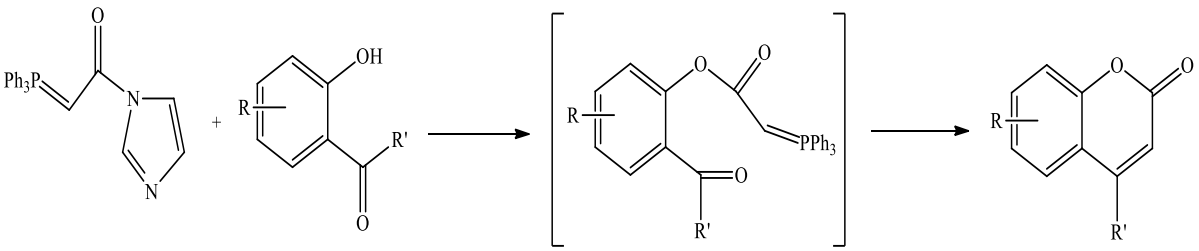
Scheme 1

a) Perkin reaction:



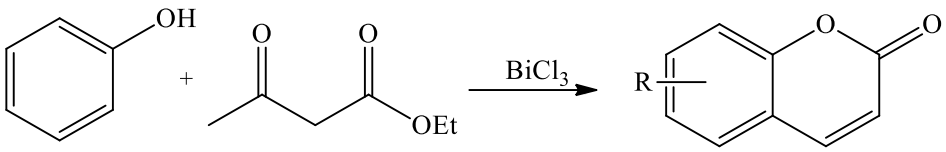
Perkin et al.; **(1868)**[9]

b) Wittig reaction:



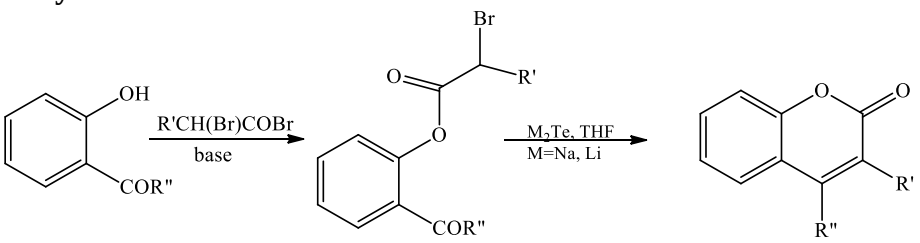
Upadhyay et al.; **(2009)**[10]

c) Pechmann reaction:



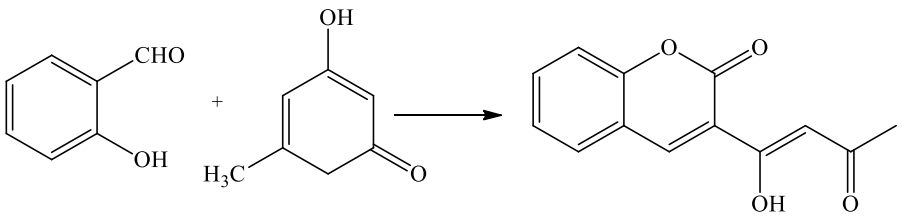
Surya, et al.; **(2005)**[11]

d) Reformatsky Reaction:



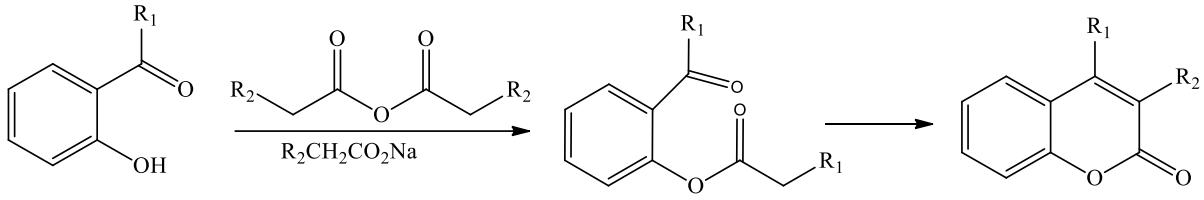
Dittmer et al.; **(2005)**[12]

e) Knoevenagel Condensation:



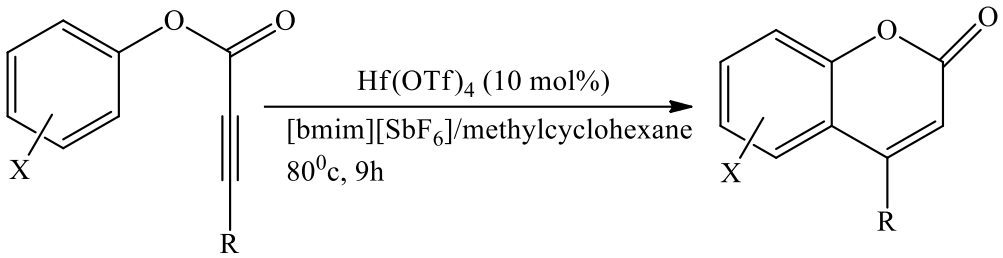
Shi et al.; **(2009)**[13]

f) Kostanecki – Robinson Reaction:



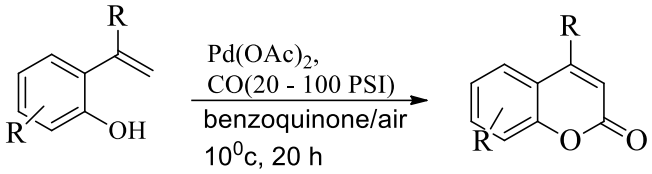
In addition, several transition metal mediated synthesis for coumarin derivatives have been exploited. For instance, Song and his co-workers have developed an intramolecular reaction using $Hf(OTf)_4$ in the presence of phase transfer catalyst such as 1-butyl-3-methylimidazolium bromide ([bmim]Br) for the formation of the 4-phenylcoumarins in moderate to good yield (Scheme 2).[14]

Scheme 2



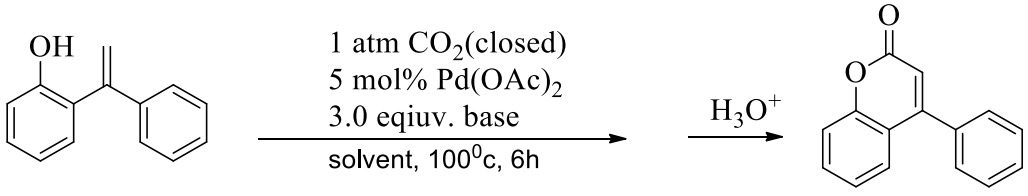
Ferguson and his co-workers synthesized a direct method by employing low pressures of CO, and air or 1, 4 - benzoquinone as the oxidant (Scheme 3).[15]

Scheme 3



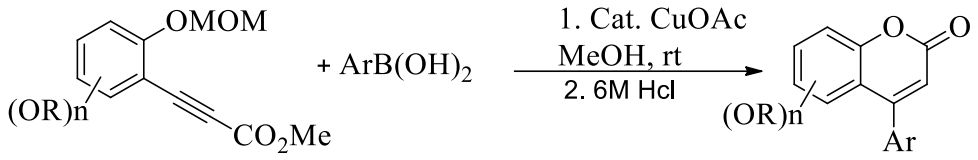
Sasano and his co-workers have developed a similar Pd-catalyzed route to produce coumarin derivatives by using atmospheric carbon dioxide (Scheme 4).[16] Furthermore, isolation of the key alkenylpalladium intermediate via C−H bond cleavage was achieved. The reaction was proposed to undergo reversible nucleophilic addition of the alkenylpalladium intermediate to CO_2.

Scheme 4



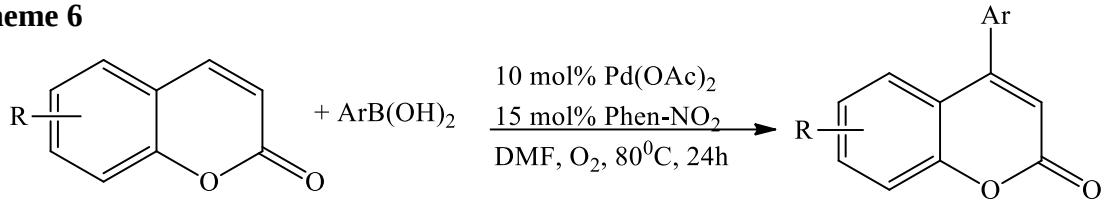
Yamamoto and Kirai have prepared 4-arylcoumarin from the reaction of protected methyl phenylpropiolates with boronic acid in the presence of CuOAc (Scheme 5).[17]

Scheme 5



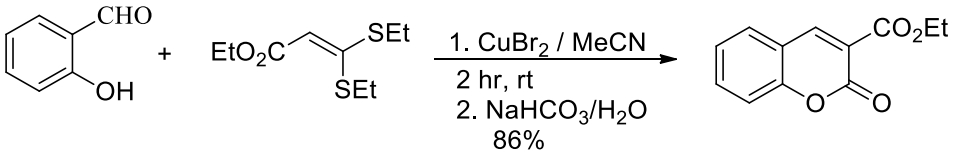
Recently, Li and his co-workers have developed an efficient protocol for the functionalization of coumarins to 4-aryl coumarins via palladium-catalyzed oxidative Heck coupling reaction of coumarins and arylboronic acids. This reaction was also found to be tolerant to various functional groups such as hydro, methoxy, diethylamino, nitro, and chloro groups (Scheme 6).[18]

Scheme 6



Analogous to this, 3-substituted coumarin are also prepared by Yuan and his co-workers have developed 3-substituted coumarin as shown in Scheme 7.[19]

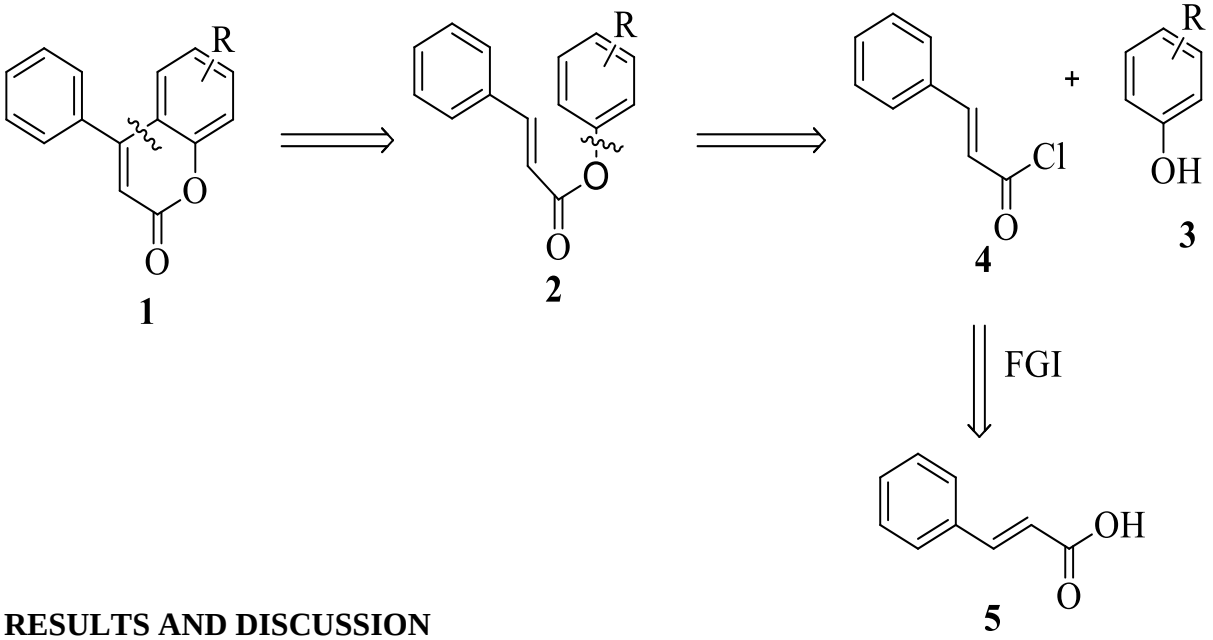
Scheme 7



OBJECTIVE

In continuation to the earlier work from this laboratory, we wish to synthesize coumarin derivatives through C-H activation. We envision that the 4-substituted coumarin (**1**) derivative can be prepared from the phenyl cinnamate (**2**). The cinnamate ester (**2**) can be achieved from the condensation of cinnamoyl chloride (**4**) with the corresponding alcohol (**3**). Our approach to coumarins is summarized retro synthetically as follows (Scheme 8):

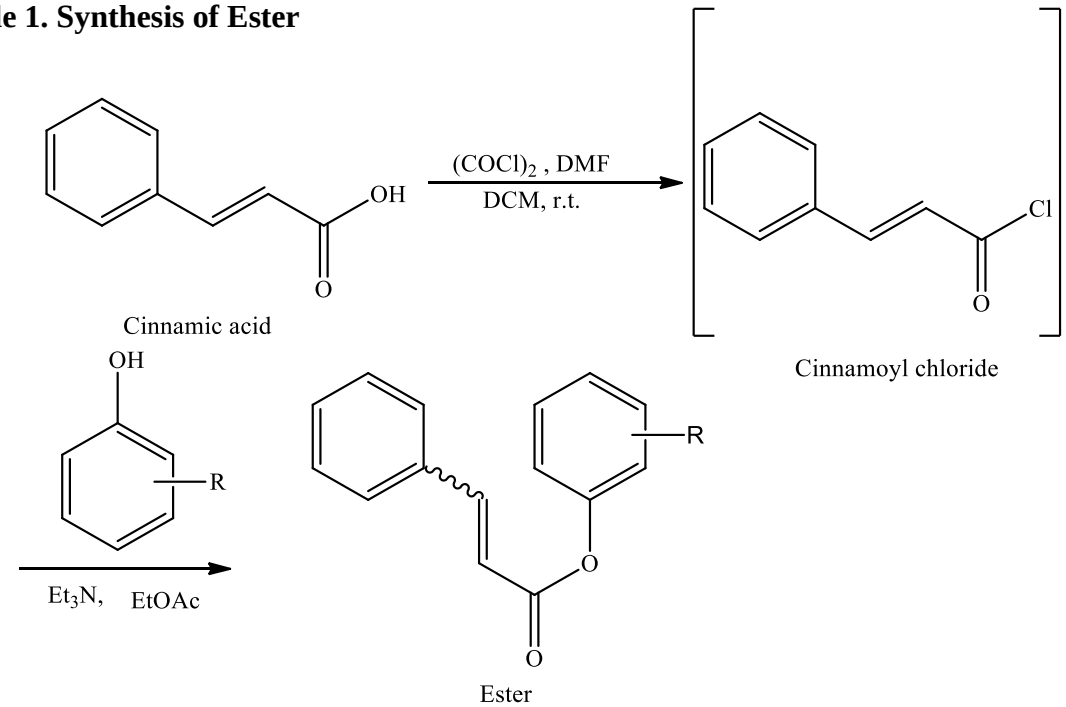
Scheme 8

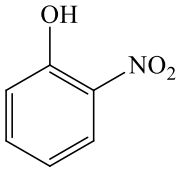
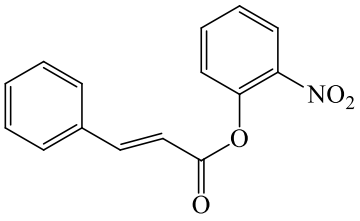
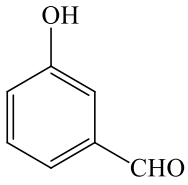
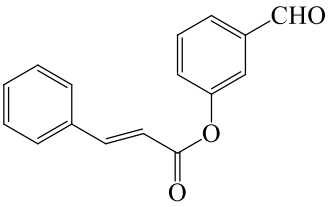
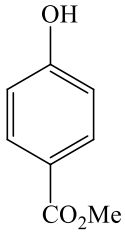
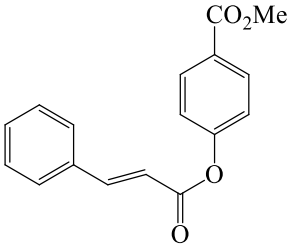
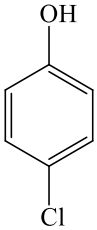
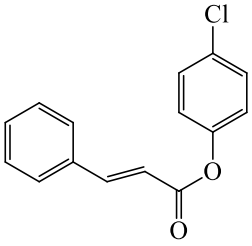


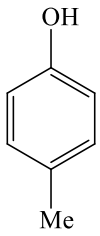
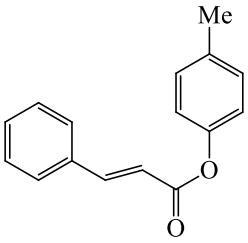
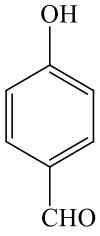
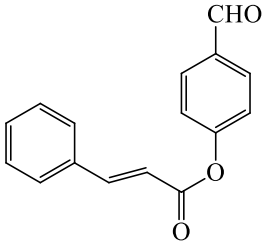
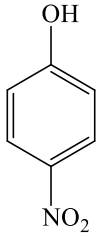
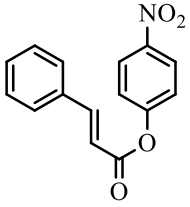
RESULTS AND DISCUSSION

We started our work with the synthesis of phenyl cinnamate (**2**). Thus on treatment of cinnamic acid (**5**) with oxalyl chloride leads to cinnamoyl chloride (**4**) intermediate which on treatment with corresponding phenol in the presence of base (Et_3N) led to the corresponding ester (**2**) which is presented in the **Table 1.** Formation of **2a** is evident from ^{1}H as well as ^{13}C NMR data. Presence of doublet at 6.673 and 7.956, benzene ring come in the range of 7.4 to 8.1 Hz, carbonyl present at 167 Hz. Following the similar procedure other ester derivatives have been prepared successfully in moderate to good yield.

Table 1. Synthesis of Ester

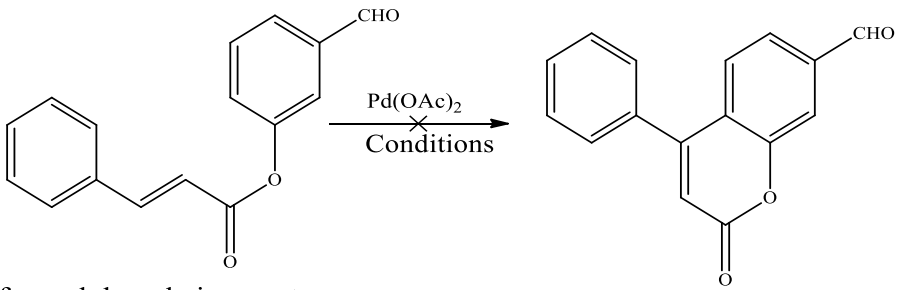


ENTRY	SUBSTITUTED PHENOL	PRODUCT	YIELD
1	 **3a**	 **2a**	90%
2	 **3b**	 **2b**	47%
3	 **3c**	 **2c**	66%
4	 **3d**	 **2d**	66%

5	 **3e**	 **2e**	65%
6	 **3f**	 **2f**	89%
7	 **3g**	 **2g**	Excess

Next we turn down our attention to convert the ester (**2**) to the corresponding coumarin derivative (**1**). Initially, we tried by using $Pd(OAc)_2$ catalyst in the presence of several oxidants oxidant such as Ag_2CO_3, $Cu(OAc)_2$, $K_2S_2O_8$ and molecular O_2. However, the starting material did not cyclized under the followed conditions to produce the corresponding coumarin derivatives (**1**).

Scheme 12



3-formylphenyl cinnamate

2-oxo-4-phenyl-2*H*-chromene-7-carbaldehyde

Conditions: i) Ag_2CO_3, MeCN

ii) $K_2S_2O_8$, PiVOH, 1, 4-dioxane

iii) DMF, Et_3N

CONCLUSION

In conclusion although we have prepared 7 number of cinnamoyl esters, till date we are unsuccessful to cyclization to the corresponding coumarin derivative. Moreover, further work in this area is going on in our lab.

EXPERIMENTAL SECTION

General Procedure for the synthesis of 2(2a-2g): Oxalyl chloride (2eq.) was added to a solution of cinnamic acid (1eq.) in dry CH_2Cl_2 (10ml) in dropwise manner, followed by addition of dry dimethyl formamide(3 drops). Then the reaction mixture was stirred for about 4 hr. Then solvent was evaporated under reduced pressure which given **4**. In presence of **4**, triethyl amine (1.1eq.) was added in dropwise manner to the solution of **3(3a-3g)** and ethyl acetate (25ml) during which precipitation was formed. And the reaction mixture of left for overnight stirring at room temperature. The completion of the reaction was checked by TLC. The organic phase was washed with water, dried over Na_2SO_4, filtered and concentrated to give crude ester **2(2a-2g)**.

NMR SPECTRAL DATA:-

2-Nitrophenyl cinnamate (2a): Yield 90%. Colourless crystal, m.p. 99^0c. ^{1}H NMR(400 MHz, $CDCl_3$): δ 8.118(m,1H), 8.097-7.956(m,1H), 7.916-7.659(m,1H), 7.613-7.594(m,2H), 7.455-7.335(m,5H), 6.713-6.673(m,1H); ^{13}C NMR(100MHz, $CDCl_3$): δ 164.37, 148.17, 144.06, 141.97, 134.72, 133.76, 131.10, 128.76, 126.55, 125.70, 125.25, 115.84.

3-Formylphenyl cinnamate (2b): Yield 47%. Colourless crystal, m.p. 95^0c. ^{1}H NMR(400 MHz, $CDCl_3$): δ 10.045(s,1H), 7.946-7.906(m,1H), 7.820-7.796(m,1H), 7.738-7.729(m,1H), 7.640-7.593(m,3H), 7.497-7.455(m,4H), 6.690-6.650(m,1H); ^{13}C NMR(100 MHz, $CDCl_3$): δ 191.2, 165.02, 151.32, 147.31, 137.70, 133.89, 130.92, 130.11, 129.01, 128.36, 127.82, 127.16, 122.42, 116.57.

(E)-Methyl 4-(cinnamoloxy) benzoate (2c): Yield 66%. Colourless crystal, m.p. 120^0c. ^{1}H NMR(400 MHz, $CDCl_3$): δ 8.8137-8.115(m,2H), 7.931-7.891(m,1H), 7.622-7.599(m,2H),

7.457-7.441(m,3H), 7.291-7.274(m,2H), 6.670-6.630(m,1H), 3.938(s,1H); ^{13}C NMR(100MHz, $CDCl_3$): δ 166.36, 164.82, 154.48, 147.28, 133.96, 131.20, 130.96, 129.06, 128.41, 127.62, 121.69, 116.76, 52.23.

4-Chlorophenyl cinnamate (2d): Yield 66%. Colourless crystal, m.p.110^{0}c. ^{1}H NMR(400MHz, $CDCl_3$): δ 7.926-7.886(m,1H), 7.628-7.604(m,2H), 7.476-7.441(m,3H), 7.418-7.379(m,2H), 7.177-7.135(m,2H), 6.666-6.626(m,1H); ^{13}C NMR(100MHz, $CDCl_3$): δ 165.20, 149.28, 147.08, 134.04, 131.16, 130.89, 129.51, 129.43, 129.05, 128.38, 123.04, 116.86.

p-Tolyl cinnamate (2e): Yield 65%. Colourless crystal, m.p.100^{0}c. ^{1}H NMR(400MHz, $CDCl_3$): δ 7.94-7.90(m,1H), 7.64-7.61(m,2H), 7.48-7.45(m,3H), 7.28-7.24(m,2H), 7.12-7.10(m,2H), 6.70-6.66(m,1H), 2.41(s,1H); ^{13}C NMR(100MHz, $CDCl_3$): δ 165.69, 148.57, 146.45, 135.47, 134.23, 130.71, 130.03, 129.04, 128.34, 121.36, 117.41, 20.97.

4-Formylphenyl cinnamate (2f): Yield 89%. Colourless crystal, m.p.98^{0}c. ^{1}H NMR(400MHz, $CDCl_3$): δ 10.021(s,1H), 7.978-7.957(m,2H), 7.7943-7.903(m,1H), 7.630-7.607(m,2H), 7.466-7.453(m,3H), 7.440-7.398(m,2H), 6.677-6.637(m,1H); ^{13}C NMR(100MHz, $CDCl_3$): δ 191.05, 164.70, 155.57, 147.59, 133.92, 133.89, 131.07, 129.10, 128.80, 128.62, 128.45, 122.46, 116.55.

4-Nitrophenyl cinnamate (2g): Yield excess. Colourless crystal, m.p.140^{0}c. ^{1}H NMR(400MHz, $CDCl_3$): δ 8.326-8.304(m, 2H), 7.958-7.918(m,1H), 7.638-7.614(m,2H), 7.486-7.461(m,3H), 7.404-7.381(m,2H), 6.675-6.635(m,1H); ^{13}C NMR(100MHz, $CDCl_3$): δ 164.36, 155.55, 148.03, 146.96, 133.70, 131.16, 128.91, 126.16, 125.19, 122.44, 116.91,

FUTURE SCOPE

These esters can be converted to cyclization.

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